TREATMENT

Predictors for the Efficacy of Naltrexone Treatment in Alcohol Dependence: Sweet Preference

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Abstract — **Aims:** To analyse the possible associations between sweet preference and the efficacy of naltrexone treatment of alcohol dependence. **Methods:** The preference for different concentrations of sucrose was evaluated in 78 participants diagnosed with alcohol dependence after treatment for 32 weeks with naltrexone or placebo without prior detoxification. **Results:** A significant difference between naltrexone and placebo groups was found in the association between the preference for higher sucrose concentrations and relapses to heavy drinking. Higher sweet preference was significantly related to successful treatment measures in the naltrexone group but not in the placebo group. **Conclusion:** Sweet preference has a strong correlation to treatment outcomes with naltrexone, and sweet preference might be used as a predictor for better treatment results in alcoholics. Our study offers one possible new explanation of the clinical observation that naltrexone is not effective for every patient.

INTRODUCTION

Many studies have proved the effectiveness of naltrexone in treating alcoholism. It reduces relapsing to heavy drinking and alcohol consumption (Kranzler and Van Kirk, 2001; Laaksonen *et al.*, 2007; Volpicelli *et al.*, 1992). Naltrexone efficacy was more robust among patients with higher baseline craving (Jaffe *et al.*, 1996; Monterosso *et al.*, 2001). Clinical benefits from naltrexone in alcoholism treatment—or associations with better responses to naltrexone—have been reported to be related to the craving for alcohol, to a positive family history for alcoholism (FH+; Jaffe *et al.*, 1996; Monterosso *et al.*, 2001; Rubio *et al.*, 2005; Volpicelli *et al.*, 1995), the age of alcohol abuse onset, the abuse of other substances (Rubio *et al.*, 2005) and the 118G allele for the opiate µ receptor (Oslin *et al.*, 2003), which has a greater affinity for endorphins (Bond *et al.*, 1998). Preference for sweets also appears to be related to the genetic factors promoting high alcohol consumption, to alcoholism (Kampov-Polevoy *et al.*, 1997, 2001) and to FH+ (Kampov-Polevoy *et al.*, 2001, 2003a, b). The sweet liking or disliking phenotype may act as a putative probe of brain opioid function and predict variations in response to naltrexone treatment (Carbutt *et al.*, 2009). The rationale for the hypothesis is that sweet preference is a measure of opioid reinforcement, and naltrexone works by blocking opioid reinforcement. Thus, a patient who is particularly sensitive to the reinforcing effects of sweet solutions may have an opioid system that produces greater reinforcement from alcohol, and thus greater therapeutic benefit from naltrexone.

Consequently, we analysed the treatment outcomes in alcohol-dependent subjects who were treated with naltrexone or placebo in a randomized clinical trial (Heinälä *et al.*, 2001) to see if their sweet preference correlates to the treatment outcomes.

PATIENTS AND METHODS

Subjects

The subjects for the sweet preference testing were recruited among patients with alcohol dependence who had completed a 32-week double-blind, placebo-controlled trial starting without prior detoxification, using 50 mg of naltrexone daily for 12 weeks and then only when needed for 20 weeks, along with therapy aimed either at coping with moderate drinking or support of complete abstinence (Heinälä *et al.*, 2001). In that study, a total of 121 persons met the inclusion criteria of (a) age 21–65 years; (b) meeting the Diagnostical and Statistical Manual of Mental Disorders version 4 (DSM-IV) criteria for alcohol dependence; (c) mean consumption of five or more drinks per day in the last 30 days; and (iv) a stable living situation and availability of a collateral reporter. Overall, 83.5% ($N = 101$) of the randomized subjects completed the first 12 weeks of the study, and 69.4% ($N = 84$) completed the whole programme. Within 1 week after the clinical trial, 84 (completers) patients were re-contacted and asked if they would be willing to participate in the sweet preference testing: 78 patients agreed to the sweet testing; of them 56 were men and 22 were women; 45 had been treated with naltrexone and 33 with placebo. The patients, sweet tester, and investigator were still blind to the investigational medicine. The alcohol consumption prior to the sweet testing was not recorded. During the sweet-testing phase, the patients were no longer taking naltrexone or placebo; however, after the sweet testing, the blinding was opened and patients had the possibility of continuing with the medication if wished.

Consent

Before entering the study, each patient signed a written informed consent. The study was conducted according to the Good Clinical Practice rules of the International Conference on Harmonisation and the Helsinki 1964 Declaration. Ethical

permission for the study was granted by the A-Clinic Foundation Ethical Committee. The randomized clinical naltrexone efficacy trial was performed during 1998–2000, and thus has no clinical trial registry number.

Sweet preference test

The test of sweet preference was conducted always by the same person at least 1.5 h after breakfast at 8:30–9:00 a.m., and at least 1 h after smoking and tooth brushing. Six different concentrations of sucrose solution (0.05, 0.10, 0.21, 0.42, 0.84 and 1.68 M; for comparison, Coca Cola is a 0.33 M sucrose solution) were each presented five times in random order (=30 testings) without telling which solution was being sampled. Patients were instructed to sip the solution, swish it around in their mouth and spit it out; then they were asked to rinse their mouth with distilled water and to proceed to the next solution. After each solution, the subject indicated 'How much do you like the taste?' by making a mark on a 200 mm horizontal visual analogue scale with the line going from 'Disliked very much' to 'Liked very much' (Kampov-Polevoy et al., 1997; Looy et al., 1992).

Sweet score

The sweet preference was calculated as the correlation between the ranking of the sucrose concentrations and the preference for that solution, using the standard method for such ordinal data, the Spearman rank–order correlation, ρ, and for brevity calling it the 'sweet score'. A sweet score of 1.00 indicates a perfect correlation with the stronger solutions being preferred over the weaker ones. The correlation measure takes into consideration all of the responses from a subject and thus is superior to earlier preference measures (e.g. just using the most liked solution) that disregarded some or most of the data. Nevertheless, in our material the sweet score was very highly correlated with the concentration most preferred ($r = 0.922$), and so results should be comparable. Furthermore, the accuracy of the correlation increases with the number of solutions tested. Therefore, we tested six sucrose solutions rather than the five used in previous studies (Kampov-Polevoy et al., 2001).

Efficacy measures

Alcohol drinking was recorded in a drinking diary, starting 1 week prior to the beginning of naltrexone or placebo administration. In the clinical trial, patients were contacted at 1, 2, 3, 5, 8, 16, 20 (telephone), 24, 28 (telephone) and 32 weeks.

Alcohol craving was measured with a Finnish translation of the Obsessive Compulsive Drinking Scale (OCDS; Anton, 2000; Anton et al., 1995) administered at the baseline, 12 and at 32 weeks. Efficacy was measured in three ways: (a) number of contacts without relapses to heavy drinking since the previous contact (defined as ≥5 drinks in one occasion at least once during the interval since the previous contact, or ≥5 drinking occasions/week since the previous contact or being intoxicated when coming for a visit); (b) reduction in alcohol drinking from the mean during baseline (1 week preceding an onset of treatment) to the mean during the final 20 weeks of treatment, measured as grams per week; and (c) reduction in OCDS scores. The efficacy measures were established prior to the trial and are similar to those used in other trials using

opioid antagonists without prior withdrawal. The complete description of the clinical trial and its results have been published by us previously (Heinälä et al., 2001). Intake and craving were previously found to decrease during naltrexone treatment with what resembles a typical extinction curve (Sinclair, 1998, 2001); therefore, the first 12 weeks were considered as an induction period and the efficacy measured as the drinking for 20 weeks from Week 13–32.

Statistics

We used multiple linear regression analyses to examine whether sweet preference predicted treatment efficacy of naltrexone. First, we tested if the sweet score predicted efficacy outcomes differently in those treated with naltrexone than in those given placebo by including the medication group by the sweet score interaction term in the model. Then we examined associations between sweet scores and efficacy outcomes in separate models for naltrexone and placebo groups.

RESULTS

There was no significant difference on any of the baseline demographic characteristics, measures of drinking, craving, prior treatment and alcoholism severity between completers or non-completers. The mean age of participants in this study was 46 years (SEM: 1).

The particular relationship between sweet scores and naltrexone efficacy can be seen in Fig. 1. Most subjects (67%) improved while on naltrexone. Among the 15 patients who instead increased their alcohol drinking, 12 had sweet scores <−0.6. All seven patients who increased by more than 100 g/week had sweet scores <−0.6; four of them had the lowest possible sweet scores.

Sweet preference associated with relapses to heavy drinking differently in the naltrexone group compared with the placebo group (P-value for interaction = 0.028). In those treated with naltrexone, lower sweet scores significantly predicted more relapses to heavy drinking during the study period (B: −1.2, 95% confidence interval [CI]: −2.3 to −0.04, $P = 0.04$), whereas there was no such association in the placebo group (B: 1.0, 95% CI: −0.60 to 2.7, $P = 0.21$). While we found no significant difference in association between sweet scores and changes in alcohol drinking or changes in the OCDS between naltrexone and placebo groups (P-values for interaction > 0.12), analyses by medication group showed a consistent pattern. In the naltrexone group, lower sweet scores significantly predicted higher mean weekly alcohol consumption in weeks 13–32 after adjusting for baseline alcohol consumption (B: −92.2, 95% CI: −165.8 to −18.6, $P = 0.015$), while there was no such association in the placebo group (B: −4.8, 95% CI: −92.6 to 83.1, $P = 0.91$). Association between the sweet score and the change in the OCDS was not significant in either group (P-values >0.33).

DISCUSSION

A strong relationship was found between lower sweet preference and poorer efficacy of naltrexone by using relapsing to heavy drinking as an outcome. To our knowledge, this is the first time that a significant association between sweet
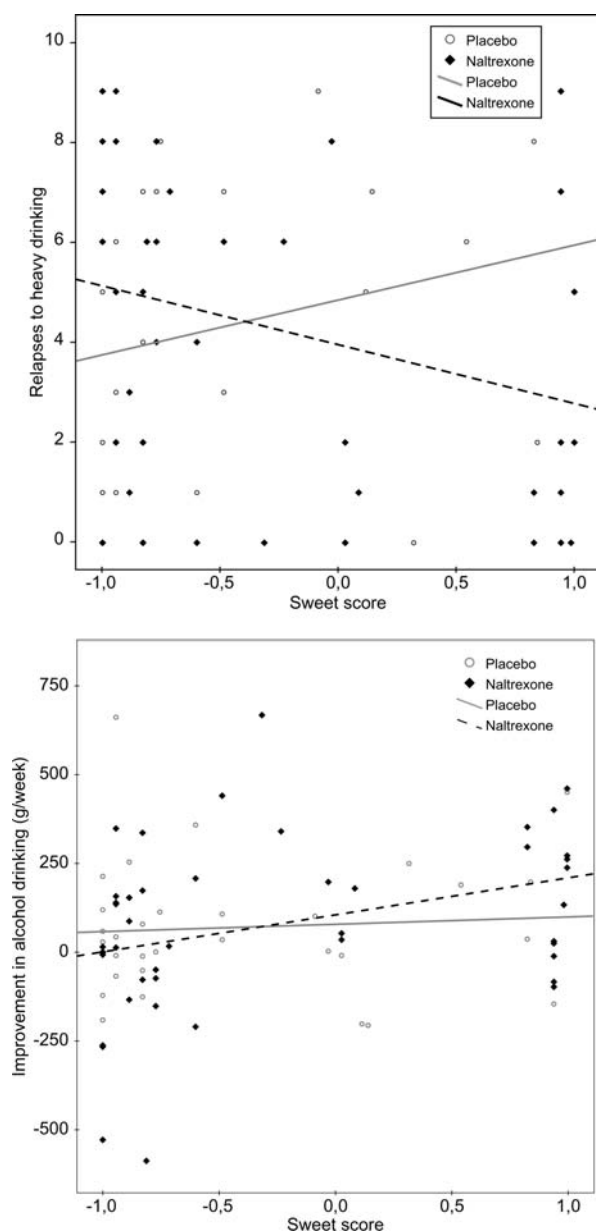
Fig. 1. The particular relationship between sweet scores and relapses to heavy drinking (upper panel) or between sweet scores and improvement in alcohol use (lower panel) during the final 20 weeks of treatment by medication group.

preference and treatment outcome has been found with regard to naltrexone efficacy. It should be noted that sweet preference here specifically means the extent to which stronger sucrose solutions are liked more than weaker sucrose solutions; subjects with lower sweet preference tend to like the weaker sucrose solutions more than they like the stronger ones.

A contributing factor to the significant difference between the naltrexone and placebo groups was that there was a tendency, although not significant, for a negative correlation between sweet preference and success in treatment among the placebo patients. This is consistent with the finding that during treatment without naltrexone, patients with alcohol dependence classified as sweet-likers at baseline are less likely to succeed in treatment (Krahn *et al*., 2006).

Reductions in sweet preference have been reported on patients treated with naltrexone (Arbisi *et al*., 1999; Krahn *et al*., 2006), and it has been considered as a side effect of naltrexone treatment (Bohn *et al*., 1994). Although we did not measure the sweet preference during the treatment, the results we obtain are opposite to what would have occurred if responding to naltrexone had caused a reduction in sweet preference: in our study, the stronger response to naltrexone (regarding reduced alcohol intake) was found in the subjects with higher sweet scores. Nevertheless, we cannot exclude the possibility that the treatment in a more indirect manner caused the observed correlations. Another confounding factor in our study is that the alcohol consumption was not measured in the week before the sweet-testing period, and it is possible that some subjects reduced or increased their drinking more than others. However, the fact that patients on active medication differ from those on placebo suggests that drinking per se may not be an issue.

A replication of the finding from this study but measuring sweet preference before treatment is necessary before it can be concluded that the sweet test could be used as a marker of naltrexone efficacy.

Our findings and other recent evidence support the conclusion that sweet preference may be linked to high alcohol consumption (Wronski *et al*., 2007) and better naltrexone treatment outcomes, and may thus be used as a predictor for a more effective treatment response for naltrexone. However, these findings warrant larger scale clinical studies.

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